

Theoretical Study of 1,3-Dipolar Cycloadditions of Nitron and Fulminic Acid with Substituted Ethylenes

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ABSTRACT: Molecular orbital calculations were performed to examine the electronic effects involved in the regioselectivity in the 1,3-dipolar cycloaddition reaction of nitron and fulminic acid. The substituted ethylene dipolarophiles were selected to represent a range of electron-donating/withdrawing abilities: amino, methyl, carbaldehyde (both in the *s*-cis and the *s*-trans conformations), and nitrile. The reactions were all asynchronous, with early transition sites. The regioselectivity was correlated with the ability of the substituent to donate or withdraw electrons. With electron-donating substituents, the substituent was directed preferentially to the oxygen end of the dipole and this shifted toward the other regioisomer as the electron-withdrawing ability of the substituent increased. © 1998 John Wiley & Sons, Inc. *J Comput Chem* 19: 1795–1804, 1998

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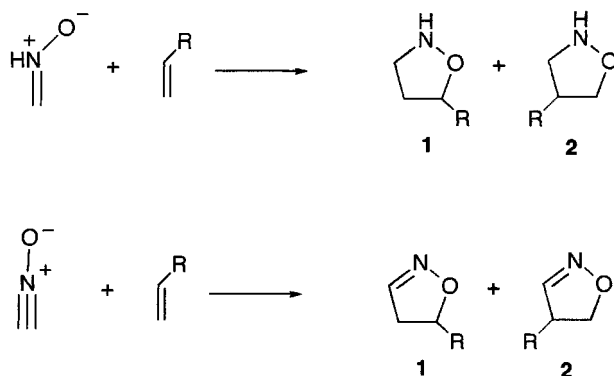
Introduction

We undertook the present study in an attempt to understand the electronic effects in the regioselectivity of the 1,3-dipolar cycloaddi-

tion reaction of nitrones and fulminic acids. The reaction is illustrated in Scheme I. The upper reaction uses nitron as the 1,3-dipole, and the lower reaction uses fulminic acid. The dipolarophiles used include propene, vinyl amine, acrolein, and acrylonitrile. These compounds cover a wide range of electron-donating and -withdrawing abilities, and what effect this will have on the regioselectivity of the reaction is a major aim of this study. It should be noted that electronic effects are not the sole cause of regioselectivity in dipolar cycloaddition reactions; that is, steric effects also play a signifi-

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SCHEME I. $R = \text{CH}_3, \text{NH}_2, \text{CN}, \text{CHO}$.

cant role. Our study, however, focuses solely on electronic effects.

Experimentally, some work has been done on the regiochemistry of the reaction.^{1,2,4,5} A careful study of the nitron cycloaddition has shown that the reaction is highly regioselective for the regioisomer in which the substituent is adjacent to the oxygen, which we refer to as regioisomer 1.^{1,2} However, most of this is caused by steric effects; when electronic effects are observable, the trends of this study agree with our calculations. Previous investigators used *C,N*-diphenyl nitron as their dipole. Dipolarophile substituents in this study included methyl, phenyl, nitrile, ethyl ester, acetyl, and formyl. The electron donor, methyl, used in this study, has the most regioisomer 1 and, as the electron donor ability decreases and the electron-withdrawing ability increases, the amount of regioisomer 2 increases.¹

Recently, an article was published on the structure of this nitron.³ Both experimentally and theoretically the structure was shown to be the *Z*-isomer, where the phenyl rings are on opposite sides of the nitron. The bulky phenyl ring on the carbon of the dipole causes steric crowding in the regioisomer with the substituent adjacent to the carbon (our regioisomer 2), preferentially causing the substituent to move to the opposite end of the dipole, yielding regioisomer 1.

A study by Sims and Houk shows that, for electron-withdrawing substituents, there is no regioselectivity if the nitron is not substituted with a bulky group on the carbon, such as when using *N-t*-butyl nitron as the dipole.⁴ This observation is consistent with our calculations. For fulminic acids, the same trends as those in the nitron investigation are observed experimentally.⁵

Computational Methods

All calculations were performed using Gaussian-92 and -94 software⁶ on a Silicon Graphics Indigo R4000 workstation. The starting geometries of all starting materials, transition states, and products were optimized with both restricted Hartree-Fock (RHF) and density functional theory using the Becke 3LYP functional.⁷ All calculations used the 6-31G* basis set. Zero-point energy corrections were ignored, because they were not expected to be significant. For example, in the nitron and propene reaction, the zero-point energy difference between the reactants and the transition state was 10 kJ/mol at the RHF level. The barrier height was 100 kJ/mol, or one order of magnitude greater.

With nitron as the dipole, there are two chiral centers in the transition state and the product, the nitrogen and the substituted carbon. The nitrogen, being pyramidal, is chiral due to the face that these are instantaneous structures, not time-averaged, as is usually assumed in nonrigid amines. The nitrogen inversion barrier prevents inversion and the hybridization of the nitrogen prohibits planarity, generating epimers at the nitrogen. In addition, there are two possible regioisomers, as shown in Scheme I. Therefore, there is a total of eight distinct structures for the transition state. To verify that the enantiomers were indeed enantiomers, all eight transition states and products were calculated using propene as the dipolarophile. Examination of the energies and structures allowed identification of the four enantiomeric pairs. Once these four pairs were located,

the remaining calculations were done with the nitrogen in the *R* configuration.

For fulminic acid, the only prochiral center is the substituted carbon, so there are only four regio-stereoisomers. Again, using propene as the dipolarophile, all transition state isomers were calculated. As expected, these four transition states consist of two regioisomeric pairs with the enantiomers having identical energies and mirror image structures. The remaining calculations were done with the substituted center in the *R* configuration.

The regioselectivity was determined using the relative activation energy; that is, the energy difference between the transition state and the isolated starting materials. By using the computed activation energies and the Arrhenius equation we can determine the relative amounts of each isomeric product. Because these are reactions in which the same pair of reactants goes to multiple products, the preexponential factor may be assumed to be identical. Therefore, the relative amounts will be proportional to the exponential factor from the Arrhenius equation. One shortcoming of this approach is that it does not take into consideration the possibility of isomerization of the product to another stereoisomer.

One other parameter that we examined was the synchronicity of the reaction. There is little doubt that the reaction is concerted,⁸ but the C—C and C—O bonds need not form at the same rate, or be equally formed in the transition state of the reaction. To do this, we determined partial bond orders in the transition state using the method of Pauling.⁹ This method determines the bond order using eq. (1):

$$\text{PBO} = 10 \left(\frac{r_{\text{TS}} - r_{\text{SB}}}{-0.17} \right) \quad (1)$$

where r_{SB} is the length of a single bond between the two atoms, as observed in the product, and r_{TS} is the length of the bond in the transition state. When Pauling formulated this theory, he used the standard lengths of single bonds. Here we instead used the bond lengths in the product, because it seems more appropriate for our purposes. It should be emphasized that Pauling's formalism was not meant to describe partial bonds in the transition state. However, there is precedent in using it for such a purpose.¹⁰ It is used in this study as a simple and straightforward qualitative measure of the extent of bond formation, which allows us to make rough estimates of synchronicity.

Results and Discussion

FRONTIER MOLECULAR ORBITALS

Sustmann and Houk¹¹ did studies on frontier molecular orbitals of 1,3-dipolar cycloaddition in the early 1970s. They proposed that the effects of substituents were based on simple HMO perturbations. Houk extended Sustmann's work by examination of orbital energies by the CNDO semiempirical method. Examination of the orbital energies obtained from this method led to certain predictions. If the reaction is controlled by the HOMO of the dipole, it is expected that the substituent be at the nonanionic end—in our case, the carbon for electron-poor dipoles and the opposite for electron-rich ones. If the dipole has a large coefficient on the nonionic end in its LUMO, electron-deficient substituents should appear near the anionic terminus, just as the electron-rich substituents do. Their results at this level of theory predict that, for nitron and fulminic acid, the products should be exclusively substituted by the oxygen. Our calculations, on the other hand, show that there is a definite trend in the regioselectivity that parallels the electron-donating or -withdrawing ability of the dipolarophile. We clearly see that the percentage of regioisomer 1 decreases as the electron-donating ability decreases and the electron-withdrawing ability increases, favoring regioisomer 2. This discrepancy could be caused by the method used to decide on the favored regioisomer. In the study cited,¹¹ orbital energies were used to determine the regioselectivity; here we examined the energy of the transition state for the formation of the regioisomer. Orbital energies were obtained using Koopman's theorem, which approximated the energy required to remove an electron from or add one to an orbital.¹²

TRANSITION STATE OF NITRONE CYCLOADDITIONS

Transition state structural and energy information is summarized in Tables I and II. The transition state for nitron and propene is illustrated in Figure 1. All other transition state structures are available as supplementary material. Examination of the Pauling partial bond order data in Table III shows that the partial bond order is different for the C—C and C—O bond in each structure. This is an indication that the reaction is asynchronous in each case.

TABLE I.
Selected Bond Lengths (Å) in 1,3-Dipolar Cycloaddition of Nitron.

| Bond | 1(R) | | 1(S) | | 2(R) | | 2(S) | |
|--------------------------------|-------|-------|-------|-------|-------|-------|-------|-------|
| | RHF | B3LYP | RHF | B3LYP | RHF | B3LYP | RHF | B3LYP |
| C ₁ —C ₂ | | | | | | | | |
| CH ₃ | 1.377 | 1.383 | 1.377 | 1.383 | 1.377 | 1.385 | 1.376 | 1.384 |
| NH ₂ | 1.378 | 1.386 | 1.383 | 1.386 | 1.374 | 1.390 | 1.374 | 1.388 |
| CN | 1.381 | 1.391 | 1.380 | 1.391 | 1.394 | 1.399 | 1.396 | 1.401 |
| CO (cis) | 1.378 | 1.382 | 1.377 | 1.387 | 1.409 | 1.401 | 1.407 | 1.400 |
| CO (trans) | 1.379 | 1.386 | 1.380 | 1.389 | 1.394 | 1.398 | 1.395 | 1.399 |
| C ₂ —C ₃ | | | | | | | | |
| CH ₃ | 2.183 | 2.194 | 2.191 | 2.207 | 2.189 | 2.197 | 2.183 | 2.191 |
| NH ₂ | 2.185 | 2.166 | 2.133 | 2.165 | 2.164 | 2.171 | 2.156 | 2.173 |
| CN | 2.149 | 2.130 | 2.133 | 2.103 | 2.360 | 2.299 | 2.380 | 2.315 |
| CO (cis) | 2.094 | 2.157 | 2.091 | 2.077 | 2.490 | 2.377 | 2.556 | 2.433 |
| CO (trans) | 2.132 | 2.125 | 2.144 | 2.117 | 2.354 | 2.309 | 2.359 | 2.314 |
| C ₃ —N | | | | | | | | |
| CH ₃ | 1.305 | 1.334 | 1.305 | 1.334 | 1.306 | 1.336 | 1.308 | 1.337 |
| NH ₂ | 1.306 | 1.338 | 1.305 | 1.334 | 1.310 | 1.341 | 1.313 | 1.345 |
| CN | 1.312 | 1.339 | 1.312 | 1.340 | 1.291 | 1.327 | 1.290 | 1.326 |
| CO (cis) | 1.317 | 1.336 | 1.315 | 1.340 | 1.280 | 1.321 | 1.276 | 1.317 |
| CO (trans) | 1.311 | 1.338 | 1.311 | 1.340 | 1.293 | 1.327 | 1.293 | 1.327 |
| N—O | | | | | | | | |
| CH ₃ | 1.288 | 1.291 | 1.288 | 1.291 | 1.283 | 1.291 | 1.285 | 1.291 |
| NH ₂ | 1.294 | 1.296 | 1.303 | 1.299 | 1.287 | 1.299 | 1.284 | 1.294 |
| CN | 1.274 | 1.279 | 1.274 | 1.273 | 1.294 | 1.301 | 1.295 | 1.302 |
| CO (cis) | 1.273 | 1.275 | 1.279 | 1.277 | 1.300 | 1.305 | 1.298 | 1.303 |
| CO (trans) | 1.279 | 1.279 | 1.278 | 1.279 | 1.295 | 1.302 | 1.295 | 1.303 |
| C ₁ —O | | | | | | | | |
| CH ₃ | 2.095 | 2.219 | 2.093 | 2.218 | 2.061 | 2.168 | 2.072 | 2.181 |
| NH ₂ | 2.097 | 2.298 | 2.227 | 2.349 | 2.043 | 2.096 | 2.090 | 2.162 |
| CN | 2.050 | 2.272 | 2.065 | 2.309 | 1.866 | 1.982 | 1.849 | 1.962 |
| CO (cis) | 2.131 | 2.402 | 2.111 | 2.384 | 1.779 | 1.928 | 1.784 | 1.931 |
| CO (trans) | 2.087 | 2.321 | 2.073 | 2.298 | 1.877 | 1.982 | 1.867 | 1.966 |

With propene and vinyl amine, both with electron-donating substituents, the C—C bond is more fully formed than the C—O bond in the transition state. This trend holds regardless of which method was used in the calculation of the transition state. The values of the partial bond orders tend to support the conclusion that the reaction proceeds through an early transition state, because all bonds in these systems are, on average, about 10% formed (bond orders of about 0.1). A general observation is that the Becke 3LYP bond orders are less than those of the RHF bond orders. In this group there is only one exception; in the vinyl amino regioiso-

mer 1(R) case, the two bond orders are almost the same, the Becke 3LYP value being only slightly larger, 0.128 vs. 0.126.

For the dipolarophiles with electron-withdrawing substituents, *cis*- and *trans*-carbaldehyde and nitrile, this same trend is only observed for regioisomer 1. For regioisomer 2, the trend reversed and the C—O bond is the one more fully formed. These bonds also are, on average, 10% formed with the main exception being the C—O bond in the carbon 2 substituted. Another general trend observed in these cases is that the C—C bond orders are greater when calculated using Becke

TABLE II. TS Energies (kJ/mol) in 1,3-Dipolar Cycloaddition of Nitron and Fulminic Acid Relative to Isolated Starting Materials.

| Dipole | 1(R) | | 1(S) | | 2(R) | | 2(S) | |
|----------------------|--------|-------|--------|-------|--------|-------|--------|-------|
| | RHF | B3LYP | RHF | B3LYP | RHF | B3LYP | RHF | B3LYP |
| Nitron | | | | | | | | |
| CH ₃ | 134.21 | 48.67 | 137.69 | 52.34 | 143.64 | 61.88 | 139.67 | 62.29 |
| NH ₂ | 100.35 | 51.17 | 113.13 | 40.54 | 149.46 | 81.42 | 156.11 | 79.35 |
| CN | 113.13 | 35.23 | 117.57 | 38.96 | 92.29 | 38.89 | 89.03 | 35.18 |
| CO (cis) | 87.62 | 5.03 | 103.88 | 24.45 | 82.89 | 29.68 | 70.50 | 16.69 |
| CO (trans) | 115.42 | 36.94 | 117.41 | 41.10 | 96.71 | 38.43 | 94.46 | 36.42 |
| Fulminic Acid | | | | | | | | |
| CH ₃ | 135.64 | 50.41 | | | 150.76 | 60.46 | | |
| NH ₂ | 110.38 | 36.87 | | | 165.99 | 77.48 | | |
| CN | 146.34 | 46.59 | | | 135.83 | 54.85 | | |
| CO (cis) | 130.48 | 35.46 | | | 132.94 | 49.18 | | |
| CO (trans) | 129.52 | 48.55 | | | 141.63 | 45.69 | | |

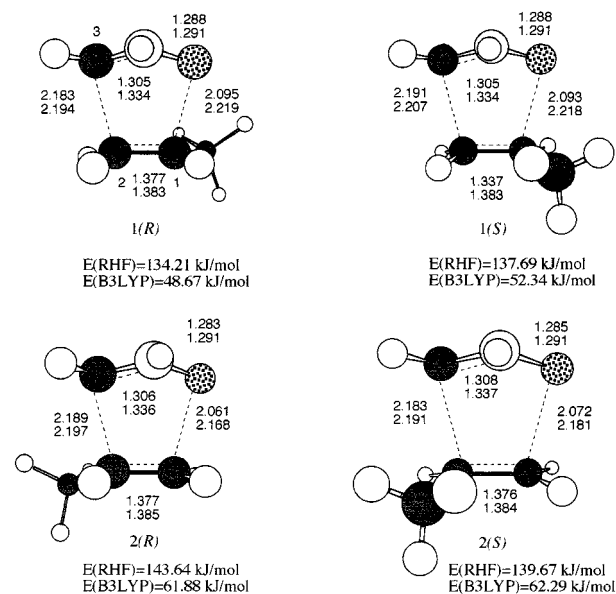


FIGURE 1. Nitron / propene transition state geometries.

3LYP than those calculated by RHF. This is not the case in the C—O bond orders, where the opposite is true.

Further support for proposing an early transition state can be obtained from the geometries of the transition states. Examination of the bonds indicates that there is little lengthening of the double bonds, supporting the proposal of an early transition state. This is true for both RHF and Becke 3LYP methods.

In conclusion, a careful analysis of the transition state structure is consistent with an early transition state for this reaction. This can be expected for an exothermic reaction, as predicted by the Hammon postulate.¹³

TRANSITION STATE OF FULMINIC ACID CYCLOADDITIONS

The structural and energy information for the transition states are summarized in Tables II and IV. As was the case with the nitrones, the only bonds listed here are the bonds in the product five-membered ring.

The Pauling partial bond orders listed in Table III show many of the same trends as the nitron data. With electron-donating substituents, propene and vinyl amine, the C—C bond is formed to a greater extent than the C—O bond. With electron-withdrawing substituents, acrolein and acrylonitrile, the situation is the same as with the electron donors of regioisomer 1, but regioisomer 2 gives the reverse result—that is, that the C—O bond is further formed than the C—C bond. There are only two exceptions to these trends. The first is for regioisomer 2 of *s-trans*-acrolein: when calculated using the RHF method, the same partial bond order is obtained, suggesting that the reaction is almost synchronous. The other exception is for regioisomer 2 of *s-cis*-acrolein: when calculated using the Becke 3LYP method, the reaction is almost synchronous. As was the case with nitrones,

TABLE III.
Pauling Partial Bond Orders.

| | Dipolarophile C ₁ —O | | Nitron C ₂ —C ₃ | | Fulminic acid | | | |
|--------------------|---------------------------------|-------|---------------------------------------|-------|-------------------|-------|--------------------------------|-------|
| | | | | | C ₁ —O | | C ₂ —C ₃ | |
| | RHF | B3LYP | RHF | B3LYP | RHF | B3LYP | RHF | B3LYP |
| Vinyl amine | | | | | | | | |
| 1(R) | 0.105 | 0.060 | 0.126 | 0.128 | 0.023 | 0.016 | 0.124 | 0.089 |
| 1(S) | 0.073 | 0.056 | 0.145 | 0.134 | | | | |
| 2(R) | 0.128 | 0.117 | 0.132 | 0.134 | 0.070 | 0.056 | 0.142 | 0.199 |
| 2(S) | 0.109 | 0.094 | 0.139 | 0.136 | | | | |
| Propene | | | | | | | | |
| 1(R) | 0.110 | 0.081 | 0.125 | 0.124 | 0.057 | 0.038 | 0.124 | 0.097 |
| 1(S) | 0.116 | 0.084 | 0.118 | 0.115 | | | | |
| 2(R) | 0.122 | 0.093 | 0.123 | 0.125 | 0.067 | 0.047 | 0.126 | 0.100 |
| 2(S) | 0.116 | 0.088 | 0.127 | 0.128 | | | | |
| Acrolein (s-cis) | | | | | | | | |
| 1(R) | 0.097 | 0.048 | 0.171 | 0.140 | 0.067 | 0.031 | 0.142 | 0.112 |
| 1(S) | 0.105 | 0.048 | 0.162 | 0.174 | | | | |
| 2(R) | 0.302 | 0.203 | 0.048 | 0.082 | 0.119 | 0.085 | 0.090 | 0.082 |
| 2(S) | 0.301 | 0.206 | 0.039 | 0.062 | | | | |
| Acrolein (s-trans) | | | | | | | | |
| 1(R) | 0.112 | 0.063 | 0.145 | 0.155 | 0.070 | 0.033 | 0.136 | 0.166 |
| 1(S) | 0.119 | 0.064 | 0.136 | 0.153 | | | | |
| 2(R) | 0.220 | 0.170 | 0.074 | 0.090 | 0.109 | 0.074 | 0.109 | 0.096 |
| 2(S) | 0.230 | 0.184 | 0.073 | 0.090 | | | | |
| Acrylonitrole | | | | | | | | |
| 1(R) | 0.122 | 0.067 | 0.140 | 0.153 | 0.075 | 0.034 | 0.141 | 0.123 |
| 1(S) | 0.120 | 0.062 | 0.141 | 0.161 | | | | |
| 2(R) | 0.219 | 0.160 | 0.071 | 0.089 | 0.121 | 0.083 | 0.099 | 0.097 |
| 2(S) | 0.229 | 0.169 | 0.067 | 0.086 | | | | |

the Pauling bond orders here too suggest an early transition state. The bond orders are generally about 10% of a full bond. Also, we note the same relative trend between the RHF and Becke LYP bond orders observed in the nitron system; that is, the RHF bond orders were greater than those determined by the Becke 3LYP method. The only exception here is that regioisomer 2 of vinyl amine has a larger bond order with Becke 3LYP than with RHF.

As with the nitrones, further support for early transition states is found in the bond lengths of the transition state. Examination of the bonds indicates that there is little lengthening of the double bonds, supporting the proposal of an early transition state. This is true for both RHF and Becke 3LYP methods.

In conclusion, structural data for the transition state of the 1,3-dipolar cycloaddition with fulminic acid are also consistent with an early transition state.

REGIOSELECTIVITY

As expected, the calculated RHF activation energies are larger than those from the Becke 3LYP calculations. These differences cause little variation in the regioselectivity of the electron donors, but, with the electron-withdrawing substituents, there is a significant difference in regioselectivity.

The regioselectivity data is shown in Table V. These results are listed according to the electron-donating/withdrawing ability of the substituent.

TABLE IV.
Selected Bond Lengths (Å) in 1,3-Dipolar Cycloaddition of Fulminic Acid.

| Bond | 1(R) | | 2(R) | |
|--------------------------------|-------|-------|-------|-------|
| | RHF | B3LYP | RHF | B3LYP |
| C ₁ —C ₂ | | | | |
| CH ₃ | 1.364 | 1.369 | 1.364 | 1.371 |
| NH ₂ | 1.368 | 1.371 | 1.364 | 1.377 |
| CN | 1.369 | 1.377 | 1.376 | 1.381 |
| CO (cis) | 1.364 | 1.371 | 1.376 | 1.378 |
| CO (trans) | 1.367 | 1.374 | 1.374 | 1.378 |
| C ₂ —C ₃ | | | | |
| CH ₃ | 2.145 | 2.224 | 2.146 | 2.223 |
| NH ₂ | 2.145 | 2.251 | 2.108 | 2.168 |
| CN | 2.106 | 2.154 | 2.225 | 2.243 |
| CO (cis) | 2.104 | 2.180 | 2.251 | 2.288 |
| CO (trans) | 2.118 | 2.169 | 2.193 | 2.238 |
| C ₃ —N | | | | |
| CH ₃ | 1.178 | 1.210 | 1.179 | 1.212 |
| NH ₂ | 1.179 | 1.208 | 1.181 | 1.218 |
| CN | 1.179 | 1.209 | 1.170 | 1.208 |
| CO (cis) | 1.179 | 1.207 | 1.170 | 1.208 |
| CO (trans) | 1.178 | 1.209 | 1.172 | 1.208 |
| N—O | | | | |
| CH ₃ | 1.229 | 1.225 | 1.227 | 1.225 |
| NH ₂ | 1.242 | 1.232 | 1.232 | 1.233 |
| CN | 1.218 | 1.216 | 1.232 | 1.229 |
| CO (cis) | 1.223 | 1.216 | 1.229 | 1.227 |
| CP (trans) | 1.222 | 1.216 | 1.233 | 1.229 |
| C ₁ —O | | | | |
| CH ₃ | 2.310 | 2.477 | 2.254 | 2.396 |
| NH ₂ | 2.579 | 2.719 | 2.239 | 2.340 |
| CN | 2.207 | 2.494 | 2.067 | 2.217 |
| CO (cis) | 2.250 | 2.524 | 2.080 | 2.220 |
| CO (trans) | 2.237 | 2.506 | 2.106 | 2.261 |

The top of the table represents the strongest electron donor (amino) going down to the most electron-withdrawing substituent (nitrile). Examination of these results shows that regioselectivity is directly related to the ability of the substituent to donate or withdraw electrons. As the electron-donating ability decreases, the percentage of regioisomer **1** decreases and regioisomer **2** increases.

For nitron, at the RHF level, vinyl amine has the best **1**:**2** ratio, moving through the other substituents in decreasing electron-donating ability to the most electron withdrawing. At the Becke 3LYP level for the electron doors, the electron-withdrawing substituents showed no selectivity.

Doing the same for fulminic acid, we see results similar to those of nitron. With this dipole, the difference in regioselectivity between the RHF and Becke 3LYP calculations is not as noticeable as in the nitron case.

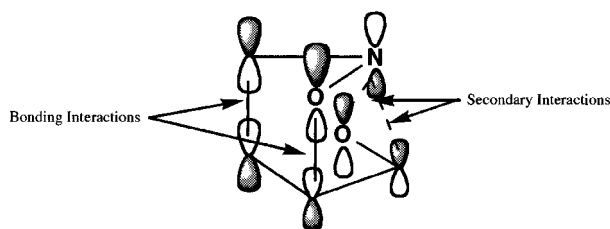
Comparison of the two systems by their regioselectivity shows that the same basic trends are observed. Vinyl amine, the best electron donor, gives the best regioselectivity, with most of the product being predicted as being regioisomer **1**. From here, the selectivity for regioisomer **1** falls off and that of regioisomer **2** increases. Using RHF calculations we see that fulminic acid selectivity ends up near 50:50, whereas, for the nitron sys-

TABLE V.
Regioselectivity Percentages in 1,3-Dipolar Cycloaddition.

| Dipolarophile | Nitron | | Fulminic acid | |
|-----------------------------|--------|-------|---------------|-------|
| | RHF | B3LYP | RHF | B3LYP |
| Vinyl amine | | | | |
| 1(<i>R</i>) | 42.7 | 30.3 | 78.3 | 75.9 |
| 1(<i>S</i>) | 31.8 | 38.7 | | |
| 2(<i>R</i>) | 13.8 | 15.1 | 21.7 | 24.1 |
| 2(<i>S</i>) | 11.8 | 15.8 | | |
| Propene | | | | |
| 1(<i>R</i>) | 27.7 | 30.4 | 58.6 | 57.1 |
| 1(<i>S</i>) | 25.5 | 27.6 | | |
| 2(<i>R</i>) | 22.3 | 21.1 | 41.4 | 42.9 |
| 2(<i>S</i>) | 24.4 | 20.9 | | |
| Acrolein (<i>s-cis</i>) | | | | |
| 1(<i>R</i>) | 23.3 | 33.7 | 51.4 | 59.6 |
| 1(<i>S</i>) | 16.0 | 21.5 | | |
| 2(<i>R</i>) | 26.0 | 19.1 | 48.6 | 40.4 |
| 2(<i>S</i>) | 34.6 | 25.7 | | |
| Acrolein (<i>s-trans</i>) | | | | |
| 1(<i>R</i>) | 19.5 | 25.7 | 43.1 | 48.0 |
| 1(<i>S</i>) | 18.7 | 23.4 | | |
| 2(<i>R</i>) | 30.1 | 24.9 | 56.9 | 52.0 |
| 2(<i>S</i>) | 31.7 | 26.0 | | |
| Acrylonitrile | | | | |
| 1(<i>R</i>) | 19.0 | 26.1 | 44.0 | 55.8 |
| 1(<i>S</i>) | 17.2 | 23.9 | | |
| 2(<i>R</i>) | 30.7 | 23.9 | 56.0 | 44.2 |
| 2(<i>S</i>) | 33.1 | 26.1 | | |

tem, the selectivity is reversed for electron-withdrawing substituents. With Becke 3LYP calculations, both nitron and fulminic acid show no selectivity with electron-withdrawing substituents. The increased preference for regioisomer 2 as the electron-withdrawing nature of the substituent increases is consistent with experimental observations.^{1,2,4,5}

An interesting observation can be made by looking at the product percentages of nitron in Table II (the substituents carbaldehyde and nitrile show some stereoselectivity of the *S* over the *R* stereoisomer of regioisomer 2, and the *R* over the *S* stereoisomer in regioisomer 1). Examination of the structures and orbitals shows that the preferred stereoisomer came from the *endo* transition state where there are secondary orbital interactions.¹³ The interaction of the LUMO of the nitron with the HOMO of the dipolarophile is favorable and leads to the stereoselectivity observed (Fig. 2).

**FIGURE 2.** Primary and secondary orbital interactions in nitron and *s-cis*-acrolein.

The differing amounts of this selectivity, small in acrylonitrile and *s-trans*-acrolein and large in *s-cis*-acrolein, can be explained by noting that, in the *s-cis*-acrolein case, the orbital on nitrogen can interact with orbitals on both the carbon and the oxygen of the dipolarophile; however, in the *s-trans*-acrolein and the nitrile cases, the nitrogen orbital was only allowed to interact with the or-

bital on the carbon of the substituent. The less favored stereoisomers (*R* for **2**, *S* for **1**) came from the *exo* transition state where there were no secondary interactions at all.

HAMMETT RELATIONS

The Hammett equation is a linear-free energy relationship that was originally determined for the ionization of substituted benzoic acids. Since it was originally devised, the Hammett equation has been expanded to cover a wide range of reactions and effects. Although the Hammett relationship is old, it is still commonly used to explain trends in organic reactions. To more fully examine the energetics of the reaction, plots of the activation energies were made relative to the Hammett σ_{meta} and σ_{para} values. These values were obtained from published tables.¹⁵ These tables include listings for methyl, amino, and cyano groups, but not for the formyl group. To do this analysis, this value was approximated by the value for the acetyl group. The values have been plotted and the results for both Hammett values are linear for regioisomer **2**; however, regioisomer **1** is not linear by regression analysis. For each regio/stereoisomer there are four possible combinations: σ_{meta} vs. the RHF E_a ; σ_{meta} vs. the DFT E_a ; σ_{para} vs. the RHF E_a ; and σ_{para} vs. the DFT E_a .

For the nitrone reaction, there are two regioisomers, each with two stereoisomers. For regioisomer **1** (*R* isomer), the correlation coefficients (*r*) for all four combinations are small. For the σ_{meta} /RHF combination, the *r* = 0.03, which indicates that there is no correlation between the these two data sets. The other RHF combination, σ_{para} /RHF, also has a very low value of *r* (0.08), which also indicates no correlation. The DFT values correlate somewhat better in this case. For σ_{meta} , *r* = -0.6, which indicates some correlation between these two sets of data; for σ_{para} , *r* = -0.7, which also shows some correlation. For regioisomer **1** (*S*-isomer), the correlation is not much better. For the σ_{meta} /RHF combination, *r* = -0.1, showing a very weak correlation. For the RHF data set, with σ_{para} , *r* = -0.1. As was the case with the *R*-isomer, the DFT correlations are better. For the σ_{meta} correlation, *r* = -0.5, and *r* = -0.4 for σ_{para} .

For regioisomer **2**, the *r* values range from -0.88 to -1. This shows that the formation of this regioisomer is correlated to the Hammett σ values used here. For the *R* isomer, the σ_{meta} correlations have the following slopes and *r* values: for

RHF calculations, -20.5 and -0.94; DFT calculations, -14.7 and -0.19. For σ_{para} the values are: RHF, -11.8 and -0.97; DFT, -8.7 and -0.97. For the *S* isomer, the RHF correlation values are: σ_{meta} , slope -24.3 and *r* = -0.91; σ_{para} , slope -14.1 and *r* = -0.95. The DFT correlation values are: σ_{meta} , slope -16.5 and *r* = -0.88; σ_{para} , slope -9.7 and *r* = -0.92.

For fulminic acid, there are also two regioisomers. However, the two stereoisomers in each regioisomer are enantiomers. Therefore, there are only two sets of data to examine, regioisomers **1** and **2**. For regioisomer **1**, as was the case with nitrone, the correlation is moderate at best. For σ_{meta} , the correlations are: RHF, *r* = 0.7, DFT, *r* = 0.1. The values for σ_{para} are: RHF, *r* = 0.8; DFT *r* = 0.2. Of these two groups, the RHF is better correlated with both σ values. Regioisomer **2** has the same level of correlation here as in the nitrone reaction. For the RHF correlations, the values are: σ_{meta} , slope -9.2 and *r* = -0.91; σ_{para} , slope -5.5 and *r* = -0.96. The DFT calculations have the following correlation values: σ_{meta} , slope -7.6 and *r* = -0.80; σ_{para} , slope -4.8 and *r* = -0.91.

The slope of these plots tells us information about the sensitivity of the reaction of the electronic effects of these substituents. For the reactions studied here, where correlation exists, all slopes are negative, indicating that the reaction is accelerated by electron-donating groups. The magnitude of the slope is larger for the nitrone case, indicating that it is more sensitive to substituent effects.

Supplementary Material

Figures 3–11 are available from the authors or from the *Journal of Computational Chemistry* website.

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